## IB. AMENDMENTS TO THE CLAIMS

Please enter the amendments to claims 12, 13, 15, and 32-34, as shown below.

1.-6. (Cancelled)

7. (Withdrawn) A transgenic non-human animal comprising a transgene stably integrated into the genome of said animal, wherein said transgene comprises a nucleotide sequence encoding carboxyl-terminal truncated apoE operably linked to a promoter such that carboxyl-terminal truncated apoE-encoding sequences are expressed, and carboxyl-terminal truncated apoE protein is synthesized, in a neuron in said animal, and wherein, as a result of said synthesis of said carboxyl-terminal truncated apoE protein, said transgenic animal develops symptoms of AD.

8. (Withdrawn) The transgenic non-human animal of claim 7, wherein the transgenic nucleotide sequence encoding carboxyl-terminal truncated apoE is overexpressed, resulting in elevated levels of carboxyl-terminal truncated apoE relative to an animal of the same species not harboring said transgene.

9. (Withdrawn) The transgenic non-human animal of claim 7, wherein the apoE is apoE4.

10. (Withdrawn) The transgenic non-human animal of claim 9, wherein said carboxyl-terminal truncated apoE4 is apoE4(Δ272-299).

11. (Withdrawn) The transgenic non-human animal of claim 7, wherein the symptom of AD is the presence of neurofibrillary tangles in a neuronal cell.

12. (**Currently amended**) A method of screening for biologically active agents that modulate a phenomenon associated with Alzheimer's disease (AD), the method comprising:

(a) contacting a cell that produces a neurotoxic carboxyl-terminal truncated apolipoprotein E (apoE) polypeptide [[apoE]] with a test agent, wherein the neurotoxic carboxyl-terminal truncated apoE polypeptide comprises amino acids 244-260 of apoE; and

(b) determining the effect of said agent on the level of the carboxyl-terminal apoE polypeptide in the cell, wherein an agent that reduces the level of the carboxyl-terminal truncated apoE polypeptide is a candidate agent for modulating a phenomenon associated with AD.

13. (**Currently amended**) The method of claim 12, wherein the cell is a cell in a non-human transgenic animal that comprises, as a transgene, a nucleic acid that comprises a nucleotide sequence encoding apoE ~~, and wherein a reduction in the level of carboxyl-terminal truncated apoE results in a reduction in neurofibrillary tangles.~~

14. (Original) The method of claim 12, wherein the cell is an *in vitro* cell.

15. (**Currently amended**) A method of screening for biologically active agents that reduce a proteolytic activity of an enzyme that catalyzes the proteolytic degradation of apoE in a neuronal cell, the method comprising:

contacting the enzyme with a test agent and a substrate that provides a detectable product when acted on by the enzyme; and

determining the effect, if any, of the test agent on formation of detectable product, wherein a reduction in the formation of detectable product indicates that the agent reduces a proteolytic activity of an enzyme that catalyzes proteolytic degradation of apoE.

16. (Original) The method of claim 15, wherein the substrate is a peptide of the formula $(P_3)_nP_2P_1$-X, wherein $P_4P_3P_2P_1$ is a peptide, wherein X is a moiety that is linked to the carboxyl terminus of the peptide, and that provides a detectable signal when cleaved from the peptide upon action by the enzyme, $P_1$ is a hydrophobic residue selected from the group consisting of leucine, phenylalanine and methionine; $P_2$ is proline; $P_3$ is alanine, and $n \geq 2$.

17. (Withdrawn) An isolated cell comprising a nucleic acid molecule that comprises a nucleotide sequence that encodes a carboxyl-terminal truncated form of apoE.

18. (Withdrawn) The isolated cell of claim 17, wherein the apoE is apoE4.

19. (Withdrawn) The isolated cell of claim 17, wherein said carboxyl-terminal truncated form of apoE4 is apoE4(Δ272-299).

20. (Withdrawn) The isolated cell of claim 17, wherein said cell is a neuronal cell.

21.-24. (Cancelled)

25. (Withdrawn) A pharmaceutical preparation comprising:

a) an inhibitor of a chymotrypsin-like protease inhibitor;

b) an agent selected from the group consisting of an acetylcholinesterase inhibitor, a non-steroidal anti-inflammatory agent, a cyclooxygenase-2 inhibitor, and a monoamine oxidase inhibitor; and

c) a pharmaceutically acceptable excipient.

26. (Withdrawn) A method of treating Alzheimer's disease, the method comprising:

a) assaying for the presence of carboxyl-terminal truncated apoE in a neuronal cell; and

b) administering an inhibitor of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell.

27. (Withdrawn) A kit comprising:

a composition comprising an inhibitor of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell; and a pharmaceutically acceptable excipient; and

instructions for administering the composition to an individual in need of thereof.

28. (Withdrawn) A method of treating Alzheimer's disease, the method comprising:

administering an inhibitor of a chymotrypsin-like serine protease in an amount effective to inhibit an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell, wherein the enzyme is inhibited and the level of neurofibrillary tangles in a neuronal cell in the individual is reduced.

29. (Withdrawn) A composition comprising:

a) an agent that inhibits an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell; and

b) a pharmaceutically acceptable excipient.

30. (Withdrawn) The composition according to claim 29, wherein the agent is selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO:1), Ala-Ala-Pro-Met (SEQ ID NO:2), Ala-Ala-Pro-Leu (SEQ ID NO:3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO:4).

31. (Cancelled)

32. (**Currently amended**) The method of claim 14, wherein the cell comprises a nucleic acid that comprises a nucleotide sequence that encodes [[a]] <u>the</u> carboxyl-terminal truncated form of apoE.

33. (**Currently amended**) The method of claim 12 [[32]], wherein the apoE is apoE4.

34. (**Currently amended**) The method of claim 33, wherein the carboxyl-terminal truncated form of apoE4 is apoE4(Δ272-299).

35. (Previously presented) The method of claim 14, wherein the cell is a neuronal cell.

36. (Previously presented) The method of claim 16, wherein X is selected from a chromogenic tag, a fluorogenic tag, a chemiluminescent tag, and a radiolabelled tag.

37. (Previously presented) The method of claim 16, wherein the peptide comprises the amino acid sequence Ala-Ala-Pro-Phe (SEQ ID NO:1.).